Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

Date:	December 20, 2011
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Drug Names:	Focalin and Focalin XR (Dexmethylphenidate)
Subject:	Angioedema and Anaphylaxis
Application Type/Number:	21278, 21802
Applicant/sponsor:	Novartis
OSE RCM #:	2011-4346

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EXECUTIVE SUMMARY

This review evaluates cases identified in the Adverse Event Reporting System (AERS) database for an association between angioedema and anaphylaxis with the use of dexmethylphenidate. In accordance with the Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) summarized post-marketing reports of adverse events associated with the use of dexmethylphenidate in pediatric patients (0-16 years of age). DPV identified one case of angioedema in this pediatric review, which prompted us to conduct an additional AERS search for reports of angioedema and anaphylaxis associated with dexmethylphenidate use across all ages. The purpose of this review is to determine if any regulatory action is necessary.

We identified a total of two cases in the AERS database reporting angioedema and anaphylaxis associated with dexmethylphenidate use across all ages, one of which was captured in the pediatric review for dexmethylphenidate. Both cases described symptoms of angioedema and anaphylaxis, such as wheezing and swollen eyelids, face, lips, mouth, throat, tongue, and/or vocal cords. These findings, coupled with the temporal association reported in both cases, support the need to update current labels for dexmethylphenidate regarding angioedema and anaphylaxis.

DPV I recommends adding angioedema and anaphylaxis to the Contraindications and Postmarketing Experience sections of dexmethylphenidate labels. Additionally, two methylphenidate products (Concerta, Daytrana) already have language regarding angioedema and anaphylaxis in their respective labels, and given that dexmethylphenidate is the d-enantiomer of methylphenidate, DPV I also recommends enhancing and harmonizing the labels of all methylphenidate products to reflect the potential risk of developing angioedema and anaphylaxis.

1 INTRODUCTION

This review evaluates cases identified in the Adverse Event Reporting System (AERS) database for an association between angioedema and anaphylaxis with the use of dexmethylphenidate. The purpose of this review is to determine if any regulatory action is necessary.

1.1 BACKGROUND

In accordance with the Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) summarized post-marketing reports of adverse events associated with the use of dexmethylphenidate in pediatric patients (0-16 years of age). DPV identified one case of angioedema in this pediatric review, which prompted us to conduct an additional AERS search for reports of angioedema and anaphylaxis associated with dexmethylphenidate use across all ages.

1.2 REGULATORY HISTORY / PRODUCT LABELING

See Appendix A for initial approval dates and labeling status of angioedema or anaphylaxis for dexmethylphenidate and methylphenidate products.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

2.1.1 ANGIOEDEMA[1]

Clinical Manifestations

Angioedema is a result of extravasation of fluid into interstitial tissues leading to localized subcutaneous or submucosal swelling. Angioedema may occur with or without urticaria, or as a component of anaphylaxis. Affected areas include loose connective tissue, such as the face, lips, and mouth. Angioedema may also involve the throat, larynx, uvula, extremities, and genitalia. Bowel wall angioedema presents as colicky abdominal pain. Below are clinical features that distinguish angioedema from other forms of edema:

- Onset in minutes to hours
- Asymmetric distribution
- Tendency not to involve gravitationally dependent areas
- Involvement of face, lips, larynx, and bowels
- Association of some forms of angioedema with other signs and symptoms of allergic reactions or anaphylaxis

Types of angioedema:

- Mast cell-mediated: There are often other signs and symptoms of mast cell mediator release, such as urticaria, flushing, generalized pruritus, bronchospasm, throat tightness, and hypotension. Onset is usually within minutes of exposure to the allergen, builds over a few hours, and resolves in 24 to 48 hours. Examples include allergic reactions to foods, drugs, latex, exercise, or insect stings.
- Bradykinin-induced: There are usually no other signs and symptoms of allergic reactions, such as urticaria or bronchospasm. Onset is usually over 24 to 36 hours and resolving within two to four days. An example is angiotensin converting enzyme inhibitor-induced angioedema.
- Idiopathic: Etiologies of unknown mechanism.

Case Inclusion Criteria

Cases were included if they described the above clinical manifestations and:

- No other etiology was apparently responsible (such as other drugs, chemicals, foods, hereditary factors, insect bites, etc.)
- Symptoms occurred within minutes to hours

2.1.2 ANAPHYLAXIS[2]

Clinical Manifestations

The clinical presentation of anaphylaxis may vary greatly in onset, appearance and course. Body systems affected typically include:

- mucocutaneous sites (pruritus, flushing, urticaria, angioedema, erythema, diaphoresis, conjunctival pruritus, lacrimation, periorbital edema)
- respiratory (stridor, choking sensation, laryngeal edema, dyspnea, tachypnea)
- cardiovascular (conduction disturbances, hypotension, cardiac arrest)

Patients often develop symptoms within 5-30 minutes after exposure to an antigen; however, reactions sometimes may not develop for several hours.

Case Inclusion Criteria

One of the following criteria satisfies the inclusion criteria for anaphylaxis or anaphylactoid reaction:

1. Clinical diagnosis of anaphylactic or anaphylactoid reaction
2. Signs of allergic process coupled with one or both of two features:
   a. respiratory difficulty
   b. cardiovascular symptoms

- The administration of epinephrine may be an indication that anaphylaxis was suspected
- No other etiology was apparently responsible (such as other drugs, chemicals, foods, hereditary factors, insect bites, etc.)
- Symptoms occurred within minutes to hours

2.2 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) database was searched with the strategy described in Table 1.

Table 1: AERS Search Strategy*	
Date	November 9, 2011
Time period	November 13, 2001[†] to November 9, 2011
Drug Names	Dexmethylphenidate, Focalin, Focalin XR, and all associated active ingredients, trade and verbatim names.
MedDRA Search Strategy	SMQ: Anaphylactic reaction (Broad) [‡] SMQ: Angioedema (Broad)[‡]

* See Appendix B for description of the AERS database.

[†] Focalin U.S. approval date

[‡] See Appendix C for a list of Preferred Terms (PTs) in the Standardized MedDRA Queries (SMQs).

2.3 LITERATURE SEARCH

We searched the PubMed database on November 23, 2011 for additional individual case reports of angioedema or anaphylaxis in association with dexmethylphenidate use. We used the following search terms without limits:

- Dexmethylphenidate, Methylphenidate [Mesh]
- Anaphylaxis [Mesh], Angioedema [Mesh], Drug hypersensitivity [Mesh]

3 RESULTS

3.1 AERS CASE SELECTION

The AERS search retrieved 34 reports, of which, 32 were not included in the final analysis for the following reasons:

- Duplicate report (N=1)
- Did not meet either case definition (N=31)
    - Reported alternative causes for PTs in SMQs (e.g., Acute myocardial infarction; Anxiety attack; Atrial septal defect; Croup; Exposure during pregnancy and breast feeding; History of cataract surgery; Infections; Left ventricular hypertrophy; Lyme disease; Near drowning; On antibiotic treatment and "passed out" during running event; Pitting edema in extremities; Raynaud's phenomenon; Stevens-Johnson Syndrome; "Toxic drug reaction"; Viral infection) [n=20]
    - Reported only labeled events (e.g., Pruritus; Rash; Urticaria) [n=6]
    - Reported PTs in SMQs without alternative causes but do not describe angioedema or anaphylaxis (e.g., *Blood pressure decreased, Coughing, Cyanosis*) [n=3]
    - Other reasons (e.g., Adverse events resolved with continued use of dexmethylphenidate; "Swollen taste buds and sensitive tongue") [n=2]

The remaining two cases were included in the case series and are described below in Table 2.

Table 2: **AERS case characteristics of angioedema and anaphylaxis associated with dexmethylphenidate received by FDA from November 13, 2001 to November 9, 2011 (N=2)**

	Case 1	Case 2
Case Number	5939635	8022129
ISR Number	4851327	7590956
Manufacturer Control Number	PHEH2005US12974	PHHY2011US57125
Age	16 years old	"Adult"
Gender	Male	Male
Report year	2005	2011
Country of occurrence	United States	United States
Report type	Expedited	Expedited
Outcome[1]	Other serious	Life-threatening

Indication	ADHD	Unknown
Dexmethylphenidate formulation	XR	XR
Dose	Unknown	5 mg
Time to onset	one hour after first dose	"couple of hours" after a dose
Reported adverse events / PTs	Angioedema; Pruritus; Swelling face; Urticaria; Wheezing	Apparent death; Dyspnoea; Eye swelling; Laryngeal oedema; Lip swelling; Oedema mouth; Pharyngeal oedema; Swelling face; Swollen tongue
Treatment for adverse events	Prescribed epinephrine, diphenhydramine, prednisone	Given diphenhydramine and "steroids"
Action taken on dexmethylphenidate	Discontinued	Unknown
Dechallenge[2]	Positive	Unknown

[1] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.
[2] Dechallenge- when the patient stopped taking the product, the adverse event abated.

3.2 LITERATURE SEARCH

We did not retrieve any case reports of dexmethylphenidate and angioedema or anaphylaxis from our literature search.

4 DISCUSSION

We identified two cases in the AERS database reporting angioedema and anaphylaxis associated with dexmethylphenidate use. Both cases described symptoms of angioedema and anaphylaxis, such as wheezing and swollen eyelids, face, lips, mouth, throat, tongue, and/or vocal cords. One case reported treatment with dexmethylphenidate discontinued, and he was prescribed diphenhydramine, epinephrine, and prednisone. The events resolved. In the second case, it was unclear whether the patient continued treatment with dexmethylphenidate but he was treated with diphenhydramine and "steroids", and reported "doing better" at the time of reporting. Although both cases reported concomitant medications associated with anaphylaxis or angioedema (e.g., citalopram, folic acid, famotidine, minocycline, and prednisone), a temporal relationship was established in both cases suggesting an association between the reported adverse events and dexmethylphenidate.

The findings from this review should be viewed in the context of the total number of AERS reports received by the FDA, as well as the drug use for both dexmethylphenidate and methylphenidate. Currently, the AERS database contains approximately 12,000 adverse event reports associated with methylphenidate, compared to dexmethylphenidate, which only has approximately 300. This is consistent with the utilization of these products across the ADHD market, with methylphenidate comprising 37% and dexmethylphenidate 6%. [11]

5 CONCLUSION

We identified a total of two cases in the AERS database reporting angioedema and anaphylaxis associated with dexmethylphenidate use across all ages, one of which was captured in the pediatric review for dexmethylphenidate. Both cases described symptoms of angioedema and anaphylaxis, such as wheezing and swollen eyelids, face, lips, mouth, throat, tongue, and/or vocal cords. These findings coupled with the temporal association reported in both cases, support the need to update current labels for dexmethylphenidate regarding angioedema and anaphylaxis.

6 RECOMMENDATIONS

DPV I recommends adding angioedema and anaphylaxis to the Contraindications and Postmarketing Experience sections of dexmethylphenidate labels. Additionally, two methylphenidate products (Concerta, Daytrana) already have language regarding angioedema and anaphylaxis in their respective labels, and given that dexmethylphenidate is the d-enantiomer of methylphenidate, DPV I also recommends enhancing and harmonizing the labels of all methylphenidate products to reflect the potential risk of developing angioedema and anaphylaxis.

7 REFERENCES

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4. Daytrana (methylphenidate patch) Prescribing Information. Shire US Inc. Wayne, PA. June 2010.
5. Focalin (dexmethylphenidate tablet) Prescribing Information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. December 2010.
6. Focalin XR (dexmethylphenidate capsule, extended release) Prescribing Information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. April 2011.
7. Metadate CD (methylphenidate capsule, extended release) Prescribing Information. UCB, Inc. Smyrna, GA. September 2010.
8. Methylin (methylphenidate solution) Prescribing Information. Shionogi Pharma, Inc. Atlanta, GA. October 2010.
9. Methylin (methylphenidate tablet, chewable) Prescribing Information. Shionogi Pharm, Inc. Atlanta, GA. October 2010.
10. Ritalin (methylphenidate tablet), Ritalin SR (methylphenidate tablet, extended release), Ritalin LA (methylphenidate tablet, extended release) Prescribing Information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. December 2010.
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8 APPENDICES

8.1 APPENDIX A. INITIAL APPROVAL DATE AND LABELING STATUS OF ANGIOEDEMA OR ANAPHYLAXIS FOR DEXMETHYLPHENIDATE AND METHYLPHENIDATE PRODUCTS [3-10]

Generic name	Brand name	NDA Number	Labeling status	Initial approval date
Dexmethylphenidate	Focalin	21278	Not labeled	November 13, 2001
	Focalin XR	21802		May 26, 2005
Methylphenidate	Concerta	21121	**Angioedema and anaphylactic reactions are labeled in the Contraindication and Postmarketing experience sections**	August 1, 2000
	Daytrana	21514	**Angioedema and anaphylaxis are labeled in the Postmarketing experience section**	April 6, 2006
	Metadate CD	21259	Not labeled	April 3, 2001
	Methylin oral solution	21419	Not labeled	December 19, 2002
	Methylin chewable tablet	21475		April 15, 2003
	Ritalin	10187	Not labeled	December 5, 1955
	Ritalin LA	21284		June 5, 2002
	Ritalin SR	18029		March 30, 1982

8.2 APPENDIX B. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly

evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Data Mining of AERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the Adverse Event Reporting System (AERS) database is utilized for data mining. MGPS analyzes the records in AERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in AERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on AERS data, limitations relating to AERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8.3 APPENDIX C. PREFERRED TERMS (PTS) IN STANDARDIZED MEDDRA QUERY (SMQ) ANGIOEDEMA AND SMQ ANAPHYLACTIC REACTIONS

Acute respiratory failure
Allergic oedema
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Angioedema
Asthma
Auricular swelling
Blood pressure decreased
Blood pressure diastolic decreased
Blood pressure systolic decreased
Breast oedema

Breast swelling
Bronchial oedema
Bronchospasm
Cardiac arrest
Cardio-respiratory arrest
Cardio-respiratory distress
Cardiovascular insufficiency
Chest discomfort
Choking
Choking sensation
Circulatory collapse
Circumoral oedema
Conjunctival oedema
Corneal oedema
Cough
Cyanosis

Diastolic hypotension
Drug hypersensitivity
Dyspnoea
Endotracheal intubation
Epiglottic oedema
Erythema
Eye oedema
Eye pruritus
Eye swelling
Eyelid oedema
Face oedema
First use syndrome
Fixed eruption
Flushing
Gastrointestinal oedema
Generalised erythema

Generalised oedema
Genital swelling
Gingival oedema
Gingival swelling
Gleich's syndrome
Hereditary angioedema
Hypersensitivity
Hyperventilation
Hypotension
Idiopathic urticaria
Injection site urticaria
Kounis syndrome
Laryngeal dyspnoea
Laryngeal obstruction
Laryngeal oedema
Laryngospasm
Laryngotracheal oedema
Limbal swelling
Lip oedema
Lip swelling
Local swelling
Localised oedema
Nasal obstruction
Nasal oedema
Nipple oedema
Nipple swelling
Obstructive airways disorder
Ocular hyperaemia
Oculorespiratory syndrome

Oedema
Oedema genital
Oedema mouth
Oedema mucosal
Oedema neonatal
Oedema peripheral
Orbital oedema
Oropharyngeal spasm
Oropharyngeal swelling
Palatal oedema
Penile oedema
Penile swelling
Periorbital oedema
Peripheral oedema neonatal
Pharyngeal oedema
Pruritus
Pruritus allergic
Pruritus generalised
Rash
Rash erythematous
Rash generalised
Rash pruritic
Respiratory arrest
Respiratory distress
Respiratory dyskinesia
Respiratory failure
Reversible airways obstruction
Scleral oedema
Scrotal oedema

Scrotal swelling
Sensation of foreign body
Shock
Skin oedema
Skin swelling
Small bowel angioedema
Sneezing
Stridor
Suffocation feeling
Swelling
Swelling face
Swollen tongue
Tachypnoea
Throat tightness
Tongue oedema
Tracheal obstruction
Tracheal oedema
Tracheostomy
Type I hypersensitivity
Upper airway obstruction
Urticaria
Urticaria cholinergic
Urticaria chronic
Urticaria papular
Vaginal oedema
Visceral oedema
Vulval oedema
Vulvovaginal swelling
Wheezing

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/s/

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12/20/2011

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